Cancer du sein métastatique et amélioration de la survie

Pr. X. Pivot
TTP/PFS Comparaisons
First line metastatic breast cancer

Monotherapy

- Herceptin + chemo
  Chan 1999

- Docetaxel
  Chan 1999

- Doxorubicin
  Chan 1999

- Paclitaxel
  Seidman 2004

- Vinorelbine
  Muñoz 2006

Polychimiotherapy

- Doxorubicin + paclitaxel
  Jassem 2001

- Xeloda + docetaxel
  O’Shaughnessy 2002

- Gemcitabine + paclitaxel
  Albain 2004

- FEC
  Zielinski 2005

- Epirubicin + docetaxel
  Pacilio 2006

Herceptin + chemo

- Herceptin + docetaxel
  Marty 2005

- Docetaxel
  Marty 2005

Avastin + chemo

- Avastin + paclitaxel
  Miller 2007

- Paclitaxel
  Miller 2007

Median PFS / TTP

0 2 4 6 8 10 12 14
(mois)

### OS as primary assessment criteria in comparative studies in MBC

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>No. of trials</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
<th>No. of trials</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PFS/TTP</td>
<td>13</td>
<td>6</td>
<td>46.2</td>
<td>3</td>
<td>23.1</td>
<td>27</td>
<td>14</td>
<td>51.9</td>
<td>6</td>
<td>22.2</td>
</tr>
<tr>
<td>TTF/TTR</td>
<td>17</td>
<td>7</td>
<td>41.2</td>
<td>1</td>
<td>5.9</td>
<td>14</td>
<td>7</td>
<td>50.0</td>
<td>5</td>
<td>35.7</td>
</tr>
<tr>
<td>RR</td>
<td>32</td>
<td>13</td>
<td>40.6</td>
<td>4</td>
<td>12.5</td>
<td>44</td>
<td>21</td>
<td>48.8</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>32</td>
<td>13</td>
<td>40.6</td>
<td>4</td>
<td>12.5</td>
<td>44</td>
<td>21</td>
<td>48.8</td>
<td>11</td>
</tr>
</tbody>
</table>


MBC, metastatic breast cancer. OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to tumour progression; TTF, time to treatment failure; TTR, time to tumour relapse.

Eribulin and clinical development. Which Phase 3 comparative studies are taking place in MBC?

<table>
<thead>
<tr>
<th>Experimental arm</th>
<th>Control arm</th>
<th>Phase</th>
<th>Patients (n)</th>
<th>Clinical status</th>
<th>Primary endpoint</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eribulin</td>
<td>Treatment of physician’s choice</td>
<td>3</td>
<td>762</td>
<td>≥3 line</td>
<td>OS</td>
<td>Publication¹</td>
</tr>
<tr>
<td>Eribulin</td>
<td>Capecitabine</td>
<td>3</td>
<td>1102</td>
<td>≥2 line</td>
<td>OS and PFS</td>
<td>Publication²</td>
</tr>
<tr>
<td>Eribulin</td>
<td>Vinorelbine</td>
<td>3</td>
<td>522 (estimated)</td>
<td>≥3 line</td>
<td>PFS</td>
<td>In progress³</td>
</tr>
<tr>
<td>Eribulin</td>
<td>Paclitaxel</td>
<td>3</td>
<td>910 (estimated)</td>
<td>1 and 2 line</td>
<td>OS</td>
<td>In progress⁴</td>
</tr>
</tbody>
</table>

OS as a primary endpoint: an original and ambitious approach for eribulin. Eribulin is the only chemotherapeutic agent with a demonstrated survival benefit for patients with heavily pre-treated MBC¹

MBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival.

ASCO Guidelines
Second line Metastatic breast cancer HER2 -

Benefit in terms of Overall Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al,</td>
<td>1995</td>
<td>vinorelbine &gt; melphalan</td>
</tr>
<tr>
<td>Nabholtz et al,</td>
<td>1999</td>
<td>docetaxel &gt; mitomycin + vinblastine.</td>
</tr>
<tr>
<td>Sparano et al,</td>
<td>2010</td>
<td>ixabepilone- capecitabine &gt; capecitabine</td>
</tr>
<tr>
<td>Albain et al,</td>
<td>2008</td>
<td>gemcitabine + paclitaxel &gt; paclitaxel</td>
</tr>
<tr>
<td>Reyno et al,</td>
<td>2004</td>
<td>BMS-217380-01 + doxorubicin &gt; doxorubicin alone</td>
</tr>
<tr>
<td>O’Shaughnessy et al,</td>
<td>2002</td>
<td>capecitabine + docetaxel &gt; docetaxel.</td>
</tr>
<tr>
<td>Cortes et al,</td>
<td>2011</td>
<td>eribulin &gt; treatment of physician’s choice</td>
</tr>
</tbody>
</table>

A Partridge et al JCO 2014
Eribulin
EMBRACE (Study 305)

Lancet 2011; 377: 914–23
Published Online
March 3, 2011
DOI:10.1016/S0140-6736(11)60070-6

Eribulin monotherapy versus treatment of physician’s choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study

Javier Cortes, Joyce O’Shaughnessy, David Loesch, Joanne L Blum, Linda T Vahdat, Katarina Petrakova, Philippe Chollet, Alexey Manikas, Veronique Diéras, Thierry Deloziere, Vladimir Vladimirov, Fatima Cardoso, Han Koh, Philippe Bougnoux, Corina E Dutcu, Seth Seegobin, Denis Mir, Nicole Meneses, Jan-tien Wanders, Chris Twelves, on behalf of the EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician’s Choice Versus E7389) investigators

Study 305 design

Patients with local advanced or metastatic breast cancer
Previously treated with two chemotherapeutic regimens for metastatic disease
Prior therapy should have included an anthracycline and a taxane

Eribulin
1.23 mg/m² (eribulin)*, Day 1 and 8 of a 21 day cycle (IV 2–5 min)*

Primary endpoint
- Overall survival

Secondary endpoints
- Progression-free survival
- Objective response
- Duration of response

Randomisation 2:1

Treatment of physician’s choice
Decided before randomisation

*Equivalent to 1.4 mg/m² eribulin mesylate IV 2-5 min.
Iv, intravenous.
Adapted from Cortes et al. Lancet 2011;377:914–923.
Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Median OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eribulin (n=508)</td>
<td>13.2</td>
</tr>
<tr>
<td>TPC (n=254)</td>
<td>10.5</td>
</tr>
<tr>
<td>HR</td>
<td>0.81</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.67, 0.96</td>
</tr>
<tr>
<td>P value*</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Conclusion

March 2011,

HALAVEN® (éribuline mésylate) indication « in Monotherpay for patients with advanced or metastatic breast cancer with a disease progression following two chemotherapy regimen at the advanced setting. Previous treatment should include Le anthracyclin and a taxane containing regimen».
## Study 301: Eribulin versus capecitabine
### Study design

**Eribulin**
- 1.23 mg/m², 2–5 min* IV
- Days 1 and 8, every 21 days

**Capecitabine**
- 1250 mg/m² orally, twice daily on days 1–14 of a 21 day cycle

### Randomisation 1:1

### Co-primary endpoints
- Overall survival and progression-free survival

### Secondary endpoints
- Quality of life
- Objective response rate
- Duration of response
- % survival at 1, 2, and 3 years
- Evaluation of symptoms related to the tumour
- Safety
- Pharmacokinetics (eribulin arm only)

### Patients
- N=1102
- Metastatic or locally advanced breast cancer
- ≤3 prior chemotherapy regimens
- ≤2 for prior chemotherapy regimens for locally advanced or metastatic disease
- Pre-exposed to an anthracycline and a taxane at any stage (neo) adjuvant, locally advanced/metastatic

### Stratification: geographical region and HER2 status

*Equivalent to 1.4 mg/m² eribulin mesylate IV 2-5 min.
HER2, human epidermal growth factor receptor 2; IV, intravenous.
Study 301: Endpoints

Co-primary efficacy endpoints were OS and PFS

- Alpha=0.05 split in 0.04 (OS) + 0.01 (PFS)

- 2 interim analyses + 1 final (OBF spending) for OS (Final Analysis at 905 deaths)

- Nominal alpha at the final analysis=0.0372

OBF, O'Brien Fleming; OS, overall survival; PFS, progression-free survival.
Study 301: OS ITT Results

Stratified Log rank and Cox Model
Overall survival was not significant

- N=1102 (554 vs 548)
- Hazard ratio=0.88
- 95% CI: 0.77–1.00
- p=0.056 > alpha=0.0372

CI, confidence interval; ITT, intent to treat; OS, overall survival.
# Study 301: Eribulin versus capecitabine OS as a function of HER2 status

<table>
<thead>
<tr>
<th>Sub-group</th>
<th>Events/N</th>
<th>Hazard ratio (95% CI)</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eribulin</td>
<td>Cape</td>
<td>Eribulin</td>
</tr>
<tr>
<td>All patients¹</td>
<td>446/554</td>
<td>459/548</td>
<td>0.88</td>
</tr>
<tr>
<td>HER2 status¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive¹</td>
<td>73/86</td>
<td>73/83</td>
<td>0.97</td>
</tr>
<tr>
<td>Negative¹</td>
<td>296/375</td>
<td>316/380</td>
<td>0.84</td>
</tr>
<tr>
<td>Unknown²</td>
<td>77/93</td>
<td>70/85</td>
<td>0.988</td>
</tr>
</tbody>
</table>

ITT population.

CI, confidence interval; HER2, human epidermal growth factor receptor 2; ITT, intent to treat; OS, overall survival.

Study 301 - OS: Lack of significance?

OS analysis adjusted for previous treatment (presence or absence trastuzumab) exhibits statistical significance.

The group of patients with HER2-positive metastatic breast cancer, more patients in the **capecitabine** group had received **trastuzumab** than in the **eribulin** group.

**Possible bias!**
OS, overall survival. Study 301 CSR, Figure F_ad_OSPFS_8.2.1.2.
Study 301: Results

Overall survival was significant in the HER2-negative subgroup

N=775 (375 vs 380)
Hazard ratio=0.84
95% CI: 0.72–0.98
p=0.03 < 0.0372

- If OS is shown to be NOT Significant in the Overall Population,

Claim for OS in a subgroup is not valid!

- Multiplicity issue: it is well known that the risk of error (Type I error) is inflated, i.e. >5%

CI, confidence interval; HER2, human epidermal growth factor receptor 2.
Study 301: Credibility of subgroup results

We need to confirm these findings in HER2-negative with new data. i.e.

Either replicate results found in HER2-negative subgroup of study 301 in a new trial and conduct a new trial for this purpose

Or perform a meta-analysis on HER2-negative patients of Studies 301 and 305

HER2, human epidermal growth factor receptor 2.
A pooled analysis of study 301 and 305 was requested by the EMA.

The data were sought to determine the relative benefit of eribulin compared with control, by HER2 and TNBC status.
Results of the pooled analysis of studies 301 and 305

Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies

Chris Twelves · Javier Cortes · Linda Vahdat · Martin Olivo · Yi He · Peter A. Kaufman · Ahmad Awada
# Pooled analysis (305+301)

## Demographic characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Eribulin (n=1062)</th>
<th>Control (n=802)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age, years (range)</td>
<td>55 (24–85)</td>
<td>54 (26–81)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>467 (44.0)</td>
<td>333 (41.5)</td>
</tr>
<tr>
<td>1</td>
<td>537 (50.6)</td>
<td>427 (53.2)</td>
</tr>
<tr>
<td>2</td>
<td>50 (4.7)</td>
<td>38 (4.7)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Disease site, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td>880 (82.9)</td>
<td>694 (86.5)</td>
</tr>
<tr>
<td>Non-visceral</td>
<td>171 (16.1)</td>
<td>101 (12.6)</td>
</tr>
<tr>
<td>Not known</td>
<td>11 (1.0)</td>
<td>7 (0.9)</td>
</tr>
<tr>
<td>HER2 status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>169 (15.9)</td>
<td>123 (15.3)</td>
</tr>
<tr>
<td>Negative</td>
<td>748 (70.4)</td>
<td>572 (71.3)</td>
</tr>
<tr>
<td>Not known</td>
<td>145 (13.7)</td>
<td>107 (13.3)</td>
</tr>
<tr>
<td>ER status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>595 (56.0)</td>
<td>449 (56.0)</td>
</tr>
<tr>
<td>Negative</td>
<td>376 (35.4)</td>
<td>288 (35.9)</td>
</tr>
<tr>
<td>Not known</td>
<td>91 (8.6)</td>
<td>65 (8.1)</td>
</tr>
<tr>
<td>Triple negative, n (%)</td>
<td>243 (22.9)</td>
<td>185 (23.1)</td>
</tr>
</tbody>
</table>

Pooled analysis (305+301)
Overall survival (ITT analysis): Confirmation of OS advantage for eribulin¹

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eribulin (n=1062)</td>
<td>15.2</td>
</tr>
<tr>
<td>Control (n=802)</td>
<td>12.8</td>
</tr>
</tbody>
</table>

| Hazard ratio | 0.85 |
| 95% CI       | 0.77–0.95 |
| p-value      | 0.003 |

In the control arm 74% of patients were treated with capecitabine²,³
CI, confidence interval; ITT, intent to treat; OS, overall survival.
CI, confidence interval; HR, hazard ratio.
### Overall survival in HER2-negative patients

<table>
<thead>
<tr>
<th>EMA¹</th>
<th>301*</th>
<th>n=595</th>
<th>HER2− ≥second line</th>
<th>Eribulin</th>
<th>Capecitabine</th>
<th>HR=0.836; 95% CI (0.70–0.99)</th>
<th>p=0.048</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA²</td>
<td>301+ 305</td>
<td>n=1320</td>
<td>HER2−</td>
<td>Eribulin</td>
<td>Control arm</td>
<td>HR=0.82; 95% CI (0.72–0.93)</td>
<td>p=0.002</td>
</tr>
<tr>
<td>EMA²</td>
<td>301+ 305</td>
<td>n=666</td>
<td>HER2− ≥second line</td>
<td>Eribulin</td>
<td>Capecitabine</td>
<td>HR=0.84; 95% CI (0.74–0.96)</td>
<td>p=0.011</td>
</tr>
</tbody>
</table>

*301, HER2 status, stratified, pre-planned HER2 analysis

Across three analyses, eribulin treatment is associated with an overall survival advantage for HER2-negative patients, regardless of the line of treatment and the control treatment arm.

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CI, confidence interval; EMA, European Medicines Agency; HER2, human epidermal growth factor receptor 2; HR, hazard ratio.
Conclusion

2011,

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2014

HALAVEN® (éribuline mésylate) indication « in Monotherpay for patients with advanced or metastatic breast cancer with a disease progression following one chemotherapy regimen at the advanced setting. Previous treatment should included anthracyclin and a taxane containing regimen». 